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Cerebral and Meningeal Multiple Myeloma After Autologous Stem Cell Transplantation. A Case Report and Review of the Literature

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Meningeal involvement of multiple myeloma is a very rare complication. Defining meningeal myelomatosis (MeM) as the presence of plasma cells in the cerebrospinal fluid in a patient with multiple myeloma, we have found 53 previously reported cases in the literature, where the diagnosis MeM has been made while the patient was alive. Using Kaplan Meier statistics we have found the median survival, from the time of diagnosis of MeM, to be 1.5 months. We report a case with MeM and possible cerebral myeloma shortly after autologous stem cell transplantation, and compare it with earlier published cases. Am. J. Hematol. 62:228–233, 1999. © 1999 Wiley-Liss, Inc.

Key words: meningeal; cerebral; myelomatosis; multiple myeloma

INTRODUCTION

Multiple myeloma is characterized by an expansion of monoclonal abnormal plasma cells in the bone marrow, and demonstration of paraprotein in plasma and urine. The survival is short, but has been improved during the last two decades by high-dose melphalan and autologous stem cell transplantation. The major clinical manifestations are related to osteolytic bone lesions, anemia, nephropathy, and an increased risk of infections. Neurological symptoms are not uncommon due to hyperviscosity, hypercalcemia, medullary compression, or paraprotein-related neuropathy, but only a few patients have a direct involvement with accumulation of myeloma cells in CNS or meninges.

CASE REPORT

A 39-year-old otherwise healthy man was admitted in June 1997, with a 6-week history of lower back pain, fatigue, headache, a weight loss of 6 kg, and opstipation. On examination he was confused, had hepatomegaly, and slight icterus.

Laboratory findings revealed Hb, 74 g/l (135–174 g/l); thrombocytes, 23×10^9/l ($150–400 \times 10^9$/l); WBC count, 15×10^9/l ($3.0–9.0 \times 10^9$/l), with 16% atypical plasma cells in peripheral blood, i.e. a total plasma cell count of 2.4×10^9/l; INR, 1.7 (0.87–1.19); LDH, 896 U/l (150–500 U/l); alkaline phosphatase, 559 U/l (80–275 U/l); calcium (ion), 2.20 mmol/l (1.15–1.29 mmol/l); creatinine, 178 μmol/l (62–133 μmol/l); uric acid, 0.84 mmol/l (0.20–0.45 mmol/l). The serum immunoassay showed raised IgA 379 μmol/l (3.2–17 μmol/l) with IgM and IgG below normal levels. There was an M-component of the IgA-λ type in the serum. Plasma β-2 microglobulin was not elevated. There was Bence Jones proteinuria with λ light chains. Bone marrow (BM) examination showed 14% IgA-λ monoclonal plasma cells, and he had multiple lytic lesions in the skull, thoracic spine, pelvis, and proximal femurs.

The diagnosis of IgA-λ multiple myeloma (MM) stage IIIB with plasma cell leukemia (PCL) was made, and treatment with prednisolone 150 mg daily was started. The patient was given an initial dose of 2 g cyclophosphamide and 3 series of VAD (vincristine, adriamycin, and dexamethasone) with good clinical and hematologi-

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cal response. In September 1997 Hb was 113 g/l , thrombocytes 242 × 10^9/l, WBC 5.9 × 10^9/l with less than 2% plasma cells in peripheral blood, IgA 33 μmol/l. BM control: 3% monoclonal plasma cells. Double autologous stem cell transplantation (AST) was planned. After mobilization with cyclophosphamide 4 g/m^2 and daily 0.3 mg of G-CSF (filgrastim), peripheral blood stem cells were collected. One week before the first AST, progression was seen with IgA 236 μmol/l, β-2 microglobulin 212 nmol/l (50–190 nmol/l), 70% monoclonal plasma cells in BM, and 10% plasma cells in peripheral blood. After conditioning with melphalan 200 mg/m^2, AST was carried out in November 1997. In January 1998 the patient was in complete remission, with no evidence of residual disease in flow cytometry examination of the BM. A second AST was planned to take place in March 1998, this time with CD 34 positive cells, selected by means of the Ceprate® SR System, (CellPro, Brussels, Belgium).

In February 1998 the patient was readmitted with pain in the neck, headache, disturbance of speech with confabulations, and weakness of the left extremities including gait and balance disturbance. He became confused, somnolent, and aggressive and had to be sedated. There was slight neck stiffness, no fever, decreased force of left extremities, normal tonus, and deep tendon reflexes and no Babinski's sign. His ventilation and circulation was stable. A magnetic resonance (MR) scan of the brain showed diffuse pathological enhancement of the meninges over the cerebrum and the cerebellum with more localized lesions in the cisterna interpeduncularis and left cerebral peduncle (Fig. 1). Treatment with IV methylprednisolone 80 mg daily was followed by some clinical improvement. A lumbar puncture revealed a CSF protein content of 2.72 g/l (0.15–0.50 g/l), glucose 2.2 mmol/l (2.2–3.9 mmol/l), and 559 nucleated cells/μl, all atypical malignant plasma cells (Fig. 2). The plasma cells were IgA-λ monoclonal by immunophenotyping. Immunoelectrophoresis of the CSF showed a monoclonal band of λ light chain, identical with the band earlier found in the urine. Neither IgA or infectious pathogens were found in the CSF. The diagnosis meningeal myelomatosis (MeM) was made, and the patient received two intrathecal chemotherapy (IT) treatments. One with 10 mg thiotepa and 50 mg hydrocortisone, and one with 12 mg methotrexate, 50 mg cytarabine, and 50 mg hydrocortisone. After the first IT treatment, the CSF contained 250 plasma cells/λl, but his condition rapidly worsened, and he became confused and developed palsies of the left third and seventh cranial nerves. He became comatose, and a CT scan showed slight progression in the localized lesions (Fig. 3). The patient died 9 days after the diagnosis of MeM, 9 months after the first admission. Permission for autopsy was not granted.

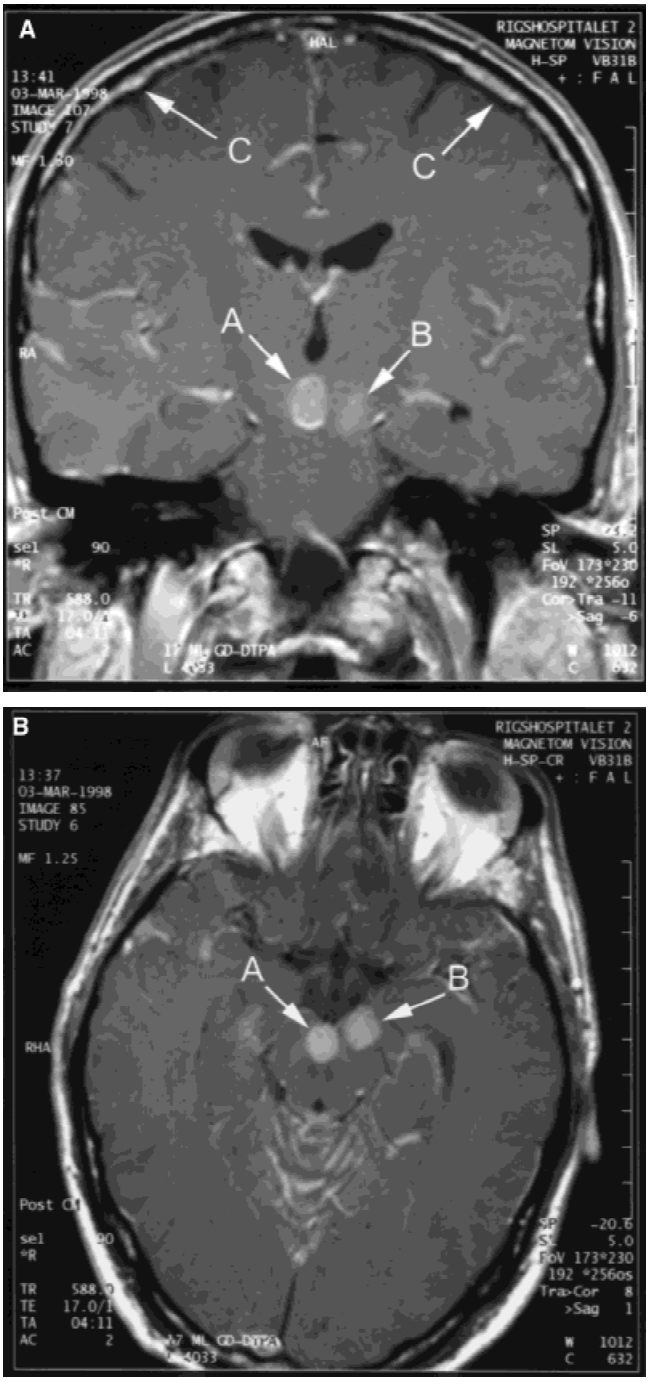

Fig. 1. Coronal (A) and axial (B) contrast-enhanced T1-weighted MR image showing diffuse enhancement in the meninges (C) and localized lesions in the cisterna interpeduncularis (A) and the left cerebral peduncle (B).

DISCUSSION

Meningeal involvement in MM is a rare complication. When reviewing the literature we have found a total of 53 cases, where the diagnosis of MeM was made while the patient was alive (1–46), our case being no. 54.

The definition of MeM used in this paper is the pres-

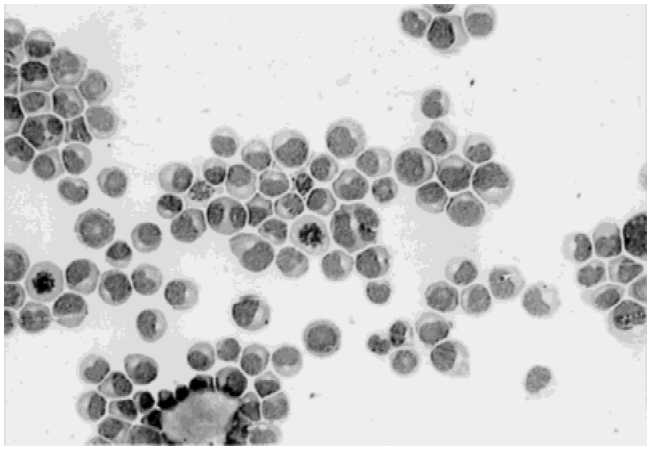

Fig. 2. Cytocentrifuge preparation of CSF with atypical malignant plasma cells (H&E × 400).

Fig. 3. Axial non-enhanced CT, demonstrating progression in the left cerebral peduncle (arrow).

ence of plasma cells in the CSF, in a patient with MM. Evidence of monoclonality of the plasma cells would be optimal [4,12], because plasma cells can be seen in the CSF in other conditions both infectious and noninfectious [4,15,47]. But if such information cannot be obtained immediately, this should not in our opinion delay treatment. The presence of a monoclonal M-component in the CSF cannot replace cytological evidence, as changes in the permeability of the blood–brain barrier can allow immunoglobulins to pass into the CSF [4,22,48].

MeM occurs in all stages of MM, but seems to be more frequent in patients with high myeloma cell mass. In 45

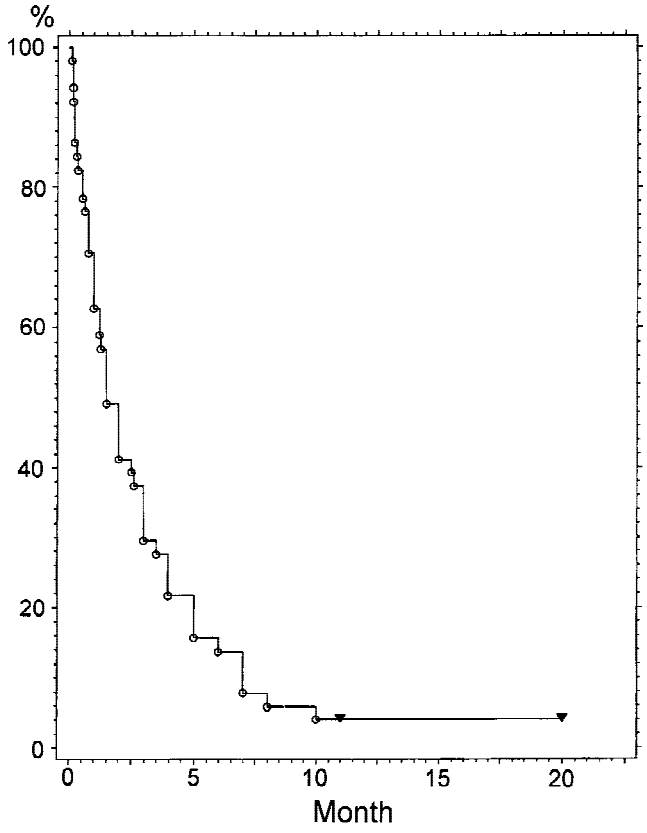

Fig. 4. Kaplan-Meier plot, based on 51 patients where survival data has been reported. (▼) Patient alive at the time of publication; (%) overall survival; (Month) time in months after diagnosis of MeM.

cases there were sufficient clinical data available to allow classification according to the staging system made by Durie and Salmon [49]; 5 cases (11%) had stage I disease, 11 (25%) stage II, and 29 (64%) stage III. MeM has earlier been correlated to high labeling index [50] and to PCL or circulating plasma cells [1,4,6,9,13,14,17,25–28]. PCL have been reported to occur with a frequency of 1–5% of patients with MM, depending on the criteria used [17,51].

Defining PCL as >20% malignant plasma cells in the differential count and/or an absolute number of $>2 \times 10^9$ plasma cells/l [51–53], we found that 4 patients (8% of all cases) had primary PCL and 6 (11%) had secondary PCL; 17 patients (31%) had circulating plasma cells before the debut of MeM. This suggests that the presence of PCL or circulating plasma cells, is a risk factor for developing MeM. Still in many cases of MeM, circulating plasma cells were never seen, suggesting hematogenous spread via lymphocytes that may be progenitors of myeloma cells [4,9,54] or lack of detection of malignant plasma cells in the blood.

The symptoms of MeM most often include mental status changes, leg weakness, cranial nerve palsies, headache, and disturbance of gait and speech [1,4,28]. The

TABLE I. Treatment, Clinical Response, and Survival*

	Treatment							
	IT	CSI	IT + CSI	IT and/or CSI	Sy. Chem	No treatment	Total	No info.
Number of patients	15	6	18	39	8	4	51	3
Clinical improvement	7	4	13	21	5	0	26	#
Survival >1.5 months	7	3	13	20	4	1	25	#

*IT, intrathecal chemotherapy; CSI, craniospinal irradiation; Sy. Chem, only systemic chemotherapy; Clinical improvement, number of patients with clinical improvement; Survival >1.5 months, number of patients surviving more than 1.5 months; No info., no information on treatment and survival.

median interval from diagnosis of MM to MeM was 8½ months, with 8 patients (15%) having MeM as presenting symptom. The longest interval was 7 years. The chemotherapy used in the interval did not show any specific pattern. The male/ female ratio was 2.4. Our patient initially had headache, which is an uncommon symptom in newly diagnosed MM, suggesting that meningeal involvement could have been present at diagnosis, but we have no cytologic or radiographic evidence to support this.

In 50 cases there was information about the type of MM with 28% being IgA, 38% IgG, 12% IgD, 14% λ light chain disease and 8% κ light chain disease. The overall κ/λ ratio was 1. IgD MM normally occurs with a frequency of less than 2% [55,56]. The total number of cases is to small to make a certain conclusion, but suggests that IgD- and IgA-MM is overrepresented in MeM patients [1,4]. In 31 cases an M-component was present in the CSF. Of the 31 cases where CT/MR was performed, 19 showed pathology which could be ascribed to MM (9 had intracerebral tumors, 7 meningeal enhancement, 3 hydrocephalus). 10 cases had normal CT/MR findings, 2 had diffuse cerebral atrophy, and 1 had changes due to an old apoplexy.

The prognosis of MeM is very poor. The patients are reported in the literature as case reports or very small series. Therefore the material is heterogeneous and there is a risk of bias for reporting mainly responding patients. However we find it acceptable to use the limited number of published cases to present survival data. On the basis of the 51 cases where information about survival was available, the median overall survival (Kaplan-Meier) from the time of diagnosis of the meningeal involvement was 1.5 months (Fig. 4).

IT and/or craniospinal irradiation (CSI) was given in 39 cases, including the present case. The IT given included methotrexate, cytarabine, and thiotepa, alone or in combination with each other, and was in most cases combined with intrathecal hydrocortisone. In some cases systemic chemotherapy was added to the IT or irradiation. In 8 cases systemic chemotherapy was given alone, and in 4 cases no chemotherapy at all was administered. The various treatments are summarized in Table I. Because of the small number of patients and the heterogeneity of the treatment schedules, no certain conclusions about the effectiveness can be made. Though it seems that the combination of IT and CSI could be the most effective schedule, many confounding factors exists, such as age, previous chemotherapy, physical condition, severity of the CNS involvement, etc. Analyzing these factors we haven't found any significant differences, thus no recommendations concerning CSI or IT can be given, while systemically administered dexamethasone induces short-term symptomatic improvement.

Only in 3 cases [37,38,40] was the patient alive at the time of publication. Three of the patients, who had earlier been reported had MeM after AST for MM [46,57]. In reviewing the literature we recommend that a lumbar puncture is performed when neurologic symptoms occur which cannot be attributed to hypercalcemia, hyperviscosity, or medullary compression. CSF should be examined for monoclonal plasma cells and M-component. CT or MR may assist in differentiating between CNS myeloma and MeM. The higher risk for MeM in PCL could indicate prophylactic treatment either with cytostatics which cross the blood–brain barrier like nitrosurea or intrathecal treatment, but this has to be documented in future studies.

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